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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/673,645	10/31/2000	Rainer Haas	100564-00035	6963

7590 11/07/2002

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EXAMINER	
MYERS, CARLA J	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/07/2002

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/673,645	HAAS ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42 and 44-52* is/are pending in the application.

4a) Of the above claim(s) *20,22-25 and 44-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19,21,26-42 and 48-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. Applicant's election with traverse of Group I in Paper No. 9 is acknowledged. The traversal is on the ground(s) that it would not require undue burden to search each of the 12 groups and all of the sequences at the same time. This is not found persuasive because it is maintained that undue burden would be required to examine the claims of groups II-VIII along with the claims of group I. A search of the distinct inventions would not be co-extensive as evidenced by the requirement for searching different keywords and nucleic acid sequences. A search of SEQ ID NO: 1 would not lead one to references teaching the sequences of SEQ ID NO: 2-12. Further, a search for references teaching methods which detect antibiotic resistance in Helicobacter would not lead one to all references teaching methods for detecting antibiotic resistance in any microorganism. Therefore, undue burden would be required to examine each of the claimed inventions. Accordingly, the requirement is still deemed proper and is therefore made FINAL.

It is noted that claims 20, 22-25, and 44-47 are withdrawn as being directed to a non-elected invention. Claim 43 was canceled in the preliminary amendment filed October 31, 2000.

2. The specification is objected to because the assigned SEQ ID NOs have not been used to identify each sequence listed, as required under 37 CFR §1.821(d). See, **for example**, pages 32-33 of the specification.

3. The specification is objected to because it does not contain, as a separate section, a brief description of the drawings. Amendment of the specification to include a separate heading for the brief description of the drawings (at, for example, page 30) is required. See 37 CFR 1.74.

4. Claims 1-19, 21, 26-42, 48-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for detecting clarithromycin resistance in H. pylori wherein the methods comprise detecting the presence of a A to G or A to C mutation at position 2058 of the 23S rRNA of H. pylori as indicative of resistance of H. pylori to clarithromycin, does not reasonably provide enablement for methods of detecting antibiotic resistance in any microorganism by detecting any mutation in any gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are very broadly drawn to methods for detecting antibiotic resistance in a microorganism wherein the methods comprise hybridizing a nucleic acid sample with a probe that is specific for any nucleic acid in any microorganism which is associated with resistance to any antibiotic. The specification teaches (see, for example, page 6) six mutations in the 23S rRNA gene which result in resistance to the antibiotics chloramphenicol, clarithromycin, clinidamycin, erythromycin, linomycin and/or streptomycin in E.coli, P. acnes, M. pneumoniae, M. intracellular and/or H. pylori. As stated in *Vaek* (20 USPQ2d 1438), the "specification must teach those of skill in the art how to make and how to use the invention as *broadly* as it is claimed" (emphasis added). The amount of guidance needed to enable the invention is related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher* 427 F. 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Predictability or lack thereof in the art refers to the ability of one of skill in the art to extrapolate the disclosed or known results to

the invention that is claimed. If one of skill in the art can readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is unpredictability in the art". With respect to the present invention, one cannot readily anticipate what additional mutations in the 23S rRNA gene and in other genes will result in resistance to antibiotics. While the prior art teaches a limited number of additional genes which confer resistance to antibiotics, the teachings in the prior art of these genes is not representative of the broadly claimed genus of any gene having any mutation which confers resistance to any antibiotic in any microorganism. The claims include an incredibly large genus of mutations and genes which have not been adequately taught in the specification. The specification does not provide sufficient guidance as to how to identify additional mutations and additional genes which confer resistance to antibiotics. To identify additional mutations associated with antibiotic resistance in microorganisms would require extensive analysis of a large genus of genes from a representative number of microorganisms for the presence of a mutation associated with resistance to any one of a large number of possible antibiotics. Such analysis is considered to be undue. The specification does not teach any mutations in any non-23S rRNA genes which confer resistance to antibiotics in Helicobacter. As set forth on page 6 of the specification, the specified 23S rRNA mutations confer resistance to different antibiotics in different microorganisms. For example, the 2058 mutation in the 23S rRNA confers resistance to clarithromycin in H. pylori,

but confers resistance to erythromycin in M. pneumoniae. Accordingly, there is no predictable means for determining which mutations confer resistance to which antibiotics in a given microorganism. While the specification exemplifies methods which analyze the 23S rRNA for the presence of mutations at positions 2032, 2057, 2058, 2059, 2503 or 2611 in 5 microorganisms, only the mutation at position 2058 has been shown to confer antibiotic resistance H. pylori. The 2058 mutation has not been shown to confer resistance to any additional antibiotics in H. pylori and the 2058 mutation has not been shown to confer antibiotic resistance to any additional species of Helicobacter. The specification has not established that the stated mutations confer resistance to all antibiotics or that these mutations confer antibiotic resistance in all microorganisms. The ability to establish a correlation between the presence of a mutation and the occurrence of antibiotic resistance is highly unpredictable and can only be determined through extensive, random, trial and error experimentation. In view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

5. Claims 31-35 and 48-50 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

6. Claims 1-19, 21, 26-42, 48-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-19, 21, 26-30 are indefinite because the steps set forth in the claims do not accomplish the objective set forth in the preamble of the claims. The claims are drawn to methods for detecting antibiotic resistance. However, the claims recite a final step of analyzing the sample in situ to determine the presence or absence of hybridization. The claims do not set forth the relationship between detecting the presence or absence of hybridization and detecting antibiotic resistance. Accordingly, it is unclear as to whether the claims are intended to be limited to methods for detecting the presence or absence of hybridization or methods for detecting antibiotic resistance. Additionally, the claims do not clarify what is intended to be encompassed by the hybridization step. That is, it is unclear if the method detects the hybridization between any 2 nucleic acid molecules or if the method detects the hybridization between the sample nucleic acid and the probe.

Claims 1-19, 21, 26-30 are indefinite over the recitation of "analyzing the sample in situ." The claims do not require that the hybridization step (b) be performed in situ and the claims do not clearly establish the relationship between step (b) and step (c). Accordingly, it is unclear as to what is intended to be encompassed by analyzing the sample in situ.

Claims 6 and 7 are indefinite and vague because it is unclear as to how the stated pathogens are to be tested and it is unclear as to whether this testing is done in place of or in addition to the in situ analysis for hybridization.

Claim 8 is indefinite over the recitation of "use is made of " because this phrase does not clearly set forth how the sample is used and how this use is related to the remainder of the claim. The claim should be amended to recite, for example: "The process of claim 1 wherein said sample is derived from human or animal tissues or body fluids." Similarly, claims 16-19, 21, 22, and 26-28 are indefinite over the recitations of "use is made of" and "use is additionally made of " because it is unclear as to how the stated probes are used in the claims and it is unclear as to whether these probes are used in addition to or in place of the probes of claim 1.

Claims 11-13 are indefinite over the recitation of "the investigation" because this phrase lacks proper antecedent basis.

Claims 11, 12, 37-42 are indefinite over the recitation of "presumptive medium" because it is unclear as to what is intended to be meant by this phrase within the context of the claim. That is, it is unclear as to what constitutes a presumptive medium.

Claim 13 is indefinite and vague over the recitation of "where appropriate, permeabilized" because the claim does not set forth the criteria for determining when it is appropriate to permeabilize the cell sample. Similarly, claims 37 and 38 are indefinite over the phrase "where appropriate."

Claim 14 is indefinite over the recitation of "such as". The phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 15 is indefinite over the recitation of "corresponding" because this is not an art recognized term to describe the relationship between two nucleic acid sequences. It is not clear whether this refers to sequence homology/similarity or to sequence complementarity and it is not clear what percentage of homology or complementarity is encompassed by "corresponding" or under what types of conditions "corresponding" nucleotides are determined. Similarly, claims 16 and 18 are indefinite over the phrase "corresponding wild-type sequence."

Claim 15 is also indefinite over the recitation of "nucleotide building blocks" because it is unclear as to what constitutes such building blocks. Are the building blocks the same as or different from or a subportion of the nucleotides? This rejection may be overcome by amendment of the claim to refer to nucleotides, rather than to nucleotide building blocks.

Claim 19 is indefinite and vague over the recitation of "nucleic acid which is associated with a wild type of the microorganism" because it is unclear as to what is intended to be meant by this phrase. For example, it is unclear as to whether the nucleic acid is in fact the wild-type sequence or is in some other unspecified way associated with a wild-type sequence.

Claim 29 is indefinite because it is unclear as to whether the analysis step is performed in addition to or in place of the analysis step of claim 1.

Claim 30 is indefinite because it is unclear as to whether the analysis step is performed in addition to or in place of the analysis step of claim 1.

Claims 31-35 and 48-50 provide for the use of a hybridization process and use of an oligonucleotide, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. It is unclear as to how the in situ hybridization method is to be used and as to how the oligonucleotides are to be used.

Claim 42 is indefinite because it is unclear as to whether indicator substance is urease or whether urease is added to the kit in addition to the indicator.

Claim 50 is indefinite over the phrase "in particular". This phrase renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 48, 50, 51 and 52 are rejected under 35 U.S.C. 102(a) as being anticipated by Pina (Journal of Clinical Microbiology (November 1998) 36(11): 3258-3290) .

It is noted that the present claims are entitled to the filing date of May 21, 1999. It is further noted that a certified translation of the foreign priority documents has not been provided

Pina teaches an oligonucleotide comprising 14 nucleotides of present SEQ ID NO: 1, wherein said probe can be used to detect antibiotic resistance (see page 3286-3287).

SEQ ID NO: 1: 5'-CGGGTCTTCCCGTCTT-3'

Pina (p43G): 5'- GGTCTTCCCGTCTTG-3'

With respect to claim 52, Pina further teaches labeling said nucleic acid with a biotin moiety (page 3286). With respect to claim 50, Pina also teaches the use of this probe with wild-type probes.

8. Claims 51 and 52 are rejected under 35 U.S.C. 102(e) as being anticipated by Stover (U.S. Patent No. 5,700,683) .

Stover teaches an oligonucleotide comprising nucleotides 4-16 of present SEQ ID NO: 1 (note that the sequence of Stover is referred to SEQ ID NO: 18 therein; see column 3).

Accordingly, Stover teaches an oligonucleotide comprising at least 10 nucleotides of SEQ ID NO: 1. With respect to claim 52, Stover further teaches labeling said nucleic acid (see, for example, column 6).

9. Claims 51 and 52 are rejected under 35 U.S.C. 102(e) as being anticipated by Meyers (U.S. Patent No. 5,925,360) .

Meyers teaches an oligonucleotide comprising nucleotides 7-17 of present SEQ ID NO: 1 (note that the sequence of Meyers is referred to SEQ ID NO: 1 therein; see column 2). Accordingly, Stover teaches an oligonucleotide comprising at least 10 nucleotides of present SEQ ID NO: 1. With respect to claim 52, Meyers further teaches labeling said nucleic acid (see, for example, column 8).

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 36-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morotomi (Journal of Clinical Microbiology (1989) 27: 2652-2655) in view of the Strategene Catalog (1988).

Morotomi teaches methods for detecting Campylobacter pylori, also known as Helicobacter pylori. The methods of Morotomi comprise growing C. pylori in a "presumptive medium", detecting the presence of C. pylori using a probe to the 16S rRNA of C. pylori, and assaying bacterial cultures via the urease test using media containing a urease indicator. It is a characteristic of the medium that it contains a nitrogen source. Accordingly, the method of Morotomi requires a "presumptive medium", a means for typing a microorganism, and an urease indicator present in a presumptive medium. Morotomi does not teach packaging these reagents into a kit.

However, reagent kits for performing detection assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Stratagene catalog discloses the general concept of kits for performing nucleic acid hybridization methods and discloses that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the reagents required to practice the method of

Morotomi in a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art wishing to detect C.pylori/H. pylori.

11. Claims 36-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pina in view of the Strategene Catalog (1988).

Pina teaches methods for detecting H. pylori. The methods of Pina comprise growing H. pylori in a "presumptive medium", detecting the presence of H. pylori using a probe to the 23S rRNA of H. pylori which detects the presence of the A2143G mutation (which is known in the art to be identical to the present A2058G mutation- the nucleotide position being different based on the numbering system utilized), and assaying bacterial cultures for their resistance to clarithromycin (see, pages 3285-3286). It is a characteristic of the medium that it contains a nitrogen source. Accordingly, the method of Pina requires a "presumptive medium", a nucleic acid probe associated with antibiotic resistance, and a means for typing an organism and detecting resistance to the antibiotic clarithromycin. It is noted that clarithromycin is considered to be an "indicator substance." Pina does not teach packaging these reagents into a kit.

However, reagent kits for performing detection assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Stratagene catalog discloses the general concept of kits for performing nucleic acid hybridization methods and discloses that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time

the invention was made to have packaged the reagents required to practice the method of Pina in a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art wishing to detect antibiotic resistant strains of H. pylori.

12. Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pina in view of the Strategene Catalog (1988) and further in view of Morotomi.

The teachings of Pina and the Stratagene catalog are presented above. The combined references do not teach including urease in the kit.

Morotomi teaches that H. pylori may be detected using a urease indicator .

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included the urease indicator taught by Morotomi in the kit in order to have provided a kit that could be used to confirm the presence of H. pylori and could also be used to detect antibiotic resistant strains of H. pylori.

13. Claims 1-19, 21, 26-35, and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pina in view of Amann.

It is noted that the present claims are entitled to the filing date of May 21, 1999. It is further noted that a certified translation of the foreign priority documents has not been provided

Pina teaches a method for detecting clarithromycin resistance to Helicobacter pylori. Pina teaches that an A to G mutation at position 2058 of the 23S rRNA of H. pylori confers resistance to the antibiotic clarithromycin . It is noted that the mutation in Pina is referred to therein as the "2143 mutation". However, this mutation is known in the art to be identical to the

present mutation at position 2058. The reference teaches both the wild-type and mutant sequence of the 23S rRNA of H. pylori. The reference teaches that the 2058 mutation can be detected by first amplifying a sample nucleic acid using PCR and then using a probe to detect the presence of the mutation in the amplified sequences. Pina does not teach detecting the 2058 mutation by performing in situ hybridization.

Amann teaches methods for detecting the presence of a mutation in bacterial DNA. In the methods of Amann, intact microbial cells are contacted with a nucleic acid probe and subjected to hybridization (see page 746). The in situ hybridization method of Amann allows one to effectively detect the presence of a single point mutation in the bacterial genome (page 765).

In view of the teachings of Amann, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Pina so as to have detected the 2058 mutation by whole-cell in situ hybridization in order to have provided a highly effective and more rapid means for detecting clarithromycin resistance in H. pylori.

With respect to claims 8, and 10-13, Amann teaches obtaining the H. pylori from patient samples and growing H. pylori in a "presumptive medium" containing an indicator. With respect to claim 9, it would have been obvious to one of ordinary skill in the art at the time the invention was made that the H. pylori sample could be directly analyzed by hybridization without culturing because Amann teaches that the whole-cell in situ hybridization method is effective for detecting a single cell. One of ordinary skill in the art would have been motivated to have omitted the

culturing step in order to have provided a more rapid means for detecting clarithromycin resistance in H. pylori. In reference to claim 13, Amann teaches fixing the cells prior to performing in situ hybridization. With respect to claims 15, and 18, Pina teaches a probe that differs from present SEQ ID NO: 1 in that it is missing three 5' nucleotides and contains an additional 3' nucleotide (see page 3286-3287):

SEQ ID NO: 1: 5'-CGGGTCTTCCCGTCTT-3'

Pina (p43G): 5'- GGTCTTCCCGTCTTG-3'

Pina also teaches that the sequence of the H. pylori 23S rRNA was well known in the art (page 3286). Further, Amann teaches that the use of oligonucleotide probes of 15 to 25 nucleotides (page 763). Given the teachings of Amann of generating probes of a length up to 25 nucleotides, it would have been obvious to one of ordinary skill in the art that additional probes could be generated which are of a longer length and which would comprise the full length sequence of SEQ ID NO: 1. In the absence of evidence of unexpected results, it would have been obvious to one of ordinary skill in the art to have generated additional probes of up to 25 nucleotides complementary to the region. With respect to claims 17, 19, and 49, Amann teaches using multiple probes simultaneously. It would have been further obvious to one of ordinary skill in the art at the time the invention was made to have included additional probes, including the wild-type probe, in order to have detected clarithromycin sensitivity in H. pylori or to detect other mutations in H. pylori. In reference to claim 21, Amann teaches the use of genus and species specific probes. It would have been further obvious to one of ordinary skill in the art to have

included a genus or species specific probe in order to have confirmed the identity of the organism. With respect to claims 29 and 30, Pina teaches that H. pylori can be microscopically and teaches quantitatively detecting clarithromycin resistance (page 3285-3286).

14. Claims 1-19, 21, 26-35 and 48-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Versalovic (Antimicrobial Agents and Chemotherapy (Feb 1996) 40: 477-480) in view of Amann (Journal of Bacteriology (Feb 1990) 172: 762-770).

Versalovic teaches a method for detecting clarithromycin resistance to Helicobacter pylori. Versalovic teaches that an A to G mutation at position 2058 of the 23S rRNA of H. pylori confers resistance to the antibiotic clarithromycin. The reference teaches both the wild-type and mutant sequence of the 23S rRNA of H. pylori (see page 478). The reference teaches that the 2058 mutation can be detected by sequencing the nucleic acids of H. pylori. However, the reference does not teach detecting the 2058 mutation by performing in situ hybridization.

Amann teaches methods for detecting the presence of a mutation in bacterial DNA. In the methods of Amann, intact microbial cells are contacted with a nucleic acid probe and subjected to hybridization (see page 746). The in situ hybridization method of Amann allows one to effectively detect the presence of a single point mutation in the bacterial genome (page 765).

In view of the teachings of Amann, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Versalovic so as to

have detected the 2058 mutation by whole-cell in situ hybridization in order to have provided a highly effective and rapid means for detecting clarithromycin resistance in H. pylori.

With respect to claims 8, and 10-13, Versalovic teaches obtaining the H. pylori from patient samples and growing H. pylori in a "presumptive medium" containing an indicator. With respect to claim 9, it would have been obvious to one of ordinary skill in the art at the time the invention was made that the H. pylori sample could be directly analyzed by hybridization without culturing because Amann teaches that the whole-cell in situ hybridization method is effective for detecting a single cell. One of ordinary skill in the art would have been motivated to have omitted the culturing step in order to have provided a more rapid means for detecting clarithromycin resistance in H. pylori. In reference to claim 13, Amann teaches fixing the cells prior to performing in situ hybridization. With respect to claim 15, Versalovic teaches a 19 bp region of 23S rRNA containing the 2058 mutation and Amann teaches that the use of oligonucleotide probes of 15 to 25 nucleotides (page 763). Accordingly, it would have been obvious to one of ordinary skill in the art to have generated probes complementary to the regions set forth by Versalovic wherein said probes are 15-25 nucleotides in length in order to have provided probes useful for detecting the 2058 mutation. With respect to claims 18, 48-49 and 51-52, probes complementary to the region set forth by Versalovic comprise at least 10 nucleotides of SEQ ID NO: 1. The sequence complementary to the region disclosed by Versalovic differs from present SEQ ID NO: 1 only in that it is missing a 3' T nucleotide. However, the sequence of the 23S rRNA of H. pylori was well known in the art at the time the

invention was made. Given the teachings of Amann of generating probes of a length up to 25 nucleotides, it would have been obvious to one of ordinary skill in the art that additional probes could be generated which are of a longer length and which would comprise the full length sequence of SEQ ID NO: 1. In the absence of evidence of unexpected results, it would have been obvious to one of ordinary skill in the art to have generated additional probes of up to 25 nucleotides complementary to the region. With respect to claims 17, 19, and 50, Amann teaches using multiple probes simultaneously. It would have been further obvious to one of ordinary skill in the art at the time the invention was made to have included additional probes, including the wild-type probe, in order to have detected clarithromycin sensitivity in H. pylori or to detect other mutations in H. pylori. In reference to claim 21, Amann teaches the use of genus and species specific probes. It would have been further obvious to one of ordinary skill in the art to have included a genus or species specific probe in order to have confirmed the identity of the organism. With respect to claims 29 and 30, Versalovic teaches examining H. pylori microscopically (page 477) and quantitatively detecting clarithromycin resistance (page 478).

15. Claims 36-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Versalovic (Antimicrobial Agents and Chemotherapy (Feb 1996) 40: 477-480) in view of Amann (Journal of Bacteriology (Feb 1990) 172: 762-770) in view of the Stratagene catalog.

The teachings of Versalovic and Amann are presented above. The combined references teach a method which requires the use of a 23S rRNA probe specific for the 2058 mutation of H.

pylori, a presumptive medium, and an indicator substance for detecting antibiotic resistance. Versalovic does not teach packaging these reagents into a kit.

However, reagent kits for performing detection assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Stratagene catalog discloses the general concept of kits for performing nucleic acid hybridization methods and discloses that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the reagents required to practice the method of Versalovic in a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art wishing to detect antibiotic resistant strains of H. pylori.

16. Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable over Versalovic in view of Amann and the Stratagene catalog and further in view of Morotomi.

The teachings of Versalovic, Amann and the Stratagene catalog are presented above. The combined references do not teach including urease in the kit.

Morotomi teaches that H. pylori may be detected using a urease indicator .

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included the urease indicator taught by Morotomi in the kit in order to have provided a kit that could be used to confirm the presence of H. pylori and could also be used to detect antibiotic resistant strains of H. pylori.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for the Technology Center is (703)-305-3014 or (703)-305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

November 4, 2002

CARLA J. MYERS
PRIMARY EXAMINER